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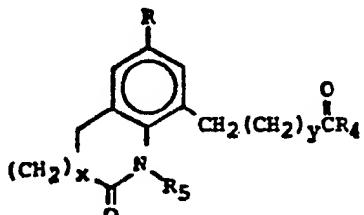
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(54) Benzobicyclic lactam acids, their derivatives, an intermediate in the preparation thereof and processes for the production thereof.

(57) Compounds having the formula I



I

wherein x and y are, independently, zero or one, are disclosed. The compounds, which have a fused aromatic carbocyclic and a saturated lactam ring of five- or six-members, their salts, esters, and amides, are useful in the treatment of senility and for reversing amnesia. Pharmaceutical compositions including these compounds, a method of preparing the compounds, and a method of treating senility and reversing amnesia are also disclosed.

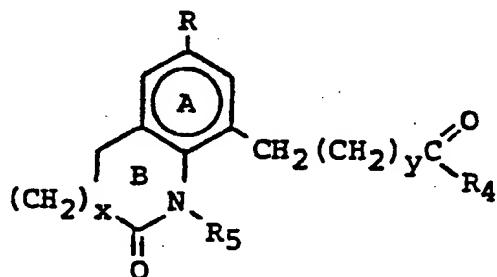
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BENZOBICYCLIC LACTAM ACIDS, THEIR DERIVATIVES,
AN INTERMEDIATE IN THE PREPARATION THEREOF AND
PROCESSES FOR THE PRODUCTION THEREOF

The present invention relates to compounds and pharmaceutical compositions useful in the treatment 10 of senility and the reversal of amnesia. More particularly, it is concerned with certain benzo-bicyclic lactam acids and their derivatives, with a method of preparing such compounds, pharmaceutical compositions including these compounds, and a method 15 of treating senility and reversing amnesia.

In its broadest aspect, the present invention relates to compounds having the structural formula I:

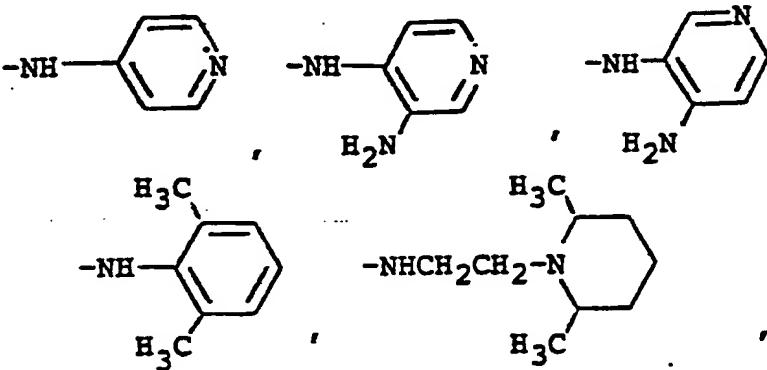


I

20 wherein x, and y are independently zero or one; R is hydrogen; halogen; hydroxyl; -OR₁ where R₁ is alkyl of from one to six carbon atoms, phenyl, or phenyl-

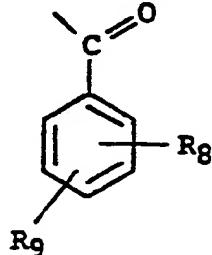
methyl; or $-\text{NR}_2\text{R}_3$ where R_2 and R_3 are independently alkyl of from one to six carbon atoms; R_4 is selected from $-\text{OH}$, together with the pharmaceutically acceptable metal, ammonium and amine

5 addition salts thereof; $-\text{OR}_1$, where R_1 is previously defined;



- $\text{NHCH}_2\text{CH}_2\text{N}[\text{CH}(\text{CH}_3)_2]_2$; and $-\text{NR}_6\text{R}_7$ where R_6 and R_7 are independently hydrogen or alkyl of from one to six carbon atoms, and the pharmaceutically acceptable acid

10 addition salts thereof; and R_5 is hydrogen or



where R_8 and R_9 are independently hydrogen; halogen; hydroxyl; $-\text{OR}_1$ where R_1 is as defined above; $\text{NR}_{10}\text{R}_{11}$

15 where R_{10} and R_{11} are independently hydrogen, alkyl of from one to six carbon atoms, or when taken together and attached to adjacent carbon atoms are $-\text{OCH}_2\text{O}-$.

Compounds of the present invention, represented

20 by structure I, comprise a class of structurally related bicyclic fused-ring compounds containing both a lactam ring and a substituted or unsubstituted aromatic ring having an attached side-chain acetic or propanoic acid group including particular salt, ester,

or amide derivatives thereof, and in which the lactam ring nitrogen atom is optionally substituted with benzoyl or substituted-benzoyl.

Although the compounds contemplated by the 5 present invention are structurally related, their nomenclature is somewhat complex. The names of the compounds are based in part on the names of the corresponding unsaturated nitrogen-containing fused-ring systems.

10 The aromatic carbocyclic ring (A as indicated in the structure above) may either be unsubstituted or is mono-substituted, preferably at the position indicated in structure I, with halogen, hydroxyl, alkoxy of from one to six carbon atoms, phenoxy, 15 phenylmethoxy, or dialkylamino in which the alkyl groups contain from one to six carbon atoms.

Also contemplated as falling within the scope of this invention are compounds in which the acetic or propanoic acid side-chain attached to the aromatic 20 carbocyclic ring is converted to pharmaceutically acceptable salts, including the salts with acceptable metal or amine cations, or is converted to esters, preferably esters derived from alcohols containing from one to six carbon atoms, phenol, and phenyl- 25 methanol, or is converted to an amide function by reaction with an amine by standard chemical activation methods. Preferred amines for this purpose are selected from the mono- and dialkylamines containing from one to six carbon atoms, particularly methyl- 30 amine, ethylamine, dimethylamine, diethylamine, and from the group consisting of N,N-disopropylaminoethylamine, 2,6-dimethylaniline, cis- or trans-2,6-dimethylpiperidinylethylamine, 4-aminopyridine, 3,4-diaminopyridine.

35 The invention also contemplates salts of those compounds falling within generic structure I in which

the group R, R₄, or R₅ contain a nitrogen atom of sufficient basicity to form acid addition salts with pharmaceutically acceptable acid anions. Included in such groups are R = dialkylamine, and R₄ = 3,4-5 diaminopyridinyl, 2,6-dimethylpiperidinylethylamino, and R₅ = alkylaminobenzoyl, dialkylaminobenzoyl, bis(alkylamino)benzoyl, and bis(dialkylamino)benzoyl.

Non-toxic, pharmaceutically acceptable acid addition salts of the foregoing classes of compounds 10 falling within the scope of this invention are formed by the reaction of the free base with any number of inorganic and organic acids including, but not necessarily limited to hydrochloric, hydrobromic, hydriodic, sulfuric, nitric, phosphoric, acetic, 15 benzoic, citric, maleic, malic, tartaric, succinic, gluconic, ascorbic, sulfamic, oxalic, pamoic, methane-sulfonic, benzenesulfonic, and related acids and mixtures thereof.

The free base forms and the salts, both anionic 20 cationic salts, of compounds of this invention may differ somewhat in their physical properties such as solubility in polar solvents, etc., but for the purposes of this invention are considered as equivalent.

25 The invention further contemplates compounds in which a substituted or unsubstituted benzoyl group is attached to the nitrogen atom of the lactam ring. The benzoyl group may be unsubstituted, or substituted with one or two groups. The benzoyl group, if substituted, is preferably substituted with hydroxyl; 30 alkoxy of from one to six carbon atoms, particularly methoxy, ethoxy; phenoxy, and phenylmethoxy; halogen, particularly, chlorine or fluorine; amino; monoalkylamino or dialkylamino of from one to six 35 carbon atoms, particularly methyl or dimethylamine; or methylenedioxy.

Stereoisomerism may be introduced into compounds of the present invention by the presence of asymmetric carbon atoms in alkyl groups forming the whole or part of substituent groups R, R₄, or R₅ as defined above.

5 The present invention contemplates all possible stereoisomers encompassed generically by structural formula I given above. The terms "stereoisomers" and "stereoisomerism" as used throughout this specification and the appended claims are to be given the meaning usually ascribed to them by practitioners of the organic chemical arts, and specifically as defined by Eliel in "Stereochemistry of Carbon Compounds," pp. 1-6, McGraw-Hill, New York, 1962.

10 The present invention contemplates all possible ring-size variants, geometrical isomers, and optical isomers of the compounds depicted generically by structural formula I given above.

15 The term "alkyl of from one to six carbon atoms" as used herein contemplates branched and unbranched 20 hydrocarbon groupings containing one to six carbon atoms as, for example, methyl, ethyl, n- and iso-propyl, n-, sec-, iso-, and tert-butyl, n-, iso-, sec-, and neopentyl, n-, sec-, and iso-hexyl, etc.

25 Compounds falling within the scope of the present invention include, but are not necessarily limited to, the following examples.

2,3-Dihydro-2-oxo-1H-indole-7-acetic acid and the pharmaceutically acceptable salts thereof.

2,3-Dihydro-1-(3-methoxybenzoyl)-2-oxo-1H-indole-30 7-acetic acid and the pharmaceutically acceptable salts thereof.

2,3-Dihydro-1-(4-methoxybenzoyl)-2-oxo-1H-indole-7-acetic acid and the pharmaceutically acceptable salts thereof.

35 2,3-Dihydro-1-(4-methoxybenzoyl)-2-oxo-1H-indole-7-propanoic acid and the pharmaceutically acceptable salts thereof.

1-[4-(Dimethylamino)benzoyl]-1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic acid and the pharmaceutically acceptable salts thereof.

1-[4-Methoxy-3-(phenylmethoxy)benzoyl]-1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic acid and the pharmaceutically acceptable salts thereof.

1-(1,3-Benzodioxol-5-ylcarbonyl)-1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic acid and the pharmaceutically acceptable salts thereof.

2,3-Dihydro-1-(4-hydroxy-3-methylbenzoyl)-2-oxo-1H-indole-7-acetic acid and the pharmaceutically acceptable salts thereof.

2,3-Dihydro-2-oxo-1H-indole-7-propanoic acid, and the pharmaceutically acceptable salts thereof.

1,2,3,4-Tetrahydro-2-oxo-8-quinolineacetic acid, and the pharmaceutically acceptable salts thereof.

1-(4-Methoxybenzoyl)-1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic acid and the pharmaceutically acceptable salts thereof.

1-Benzoyl-2,3-dihydro-2-oxo-1H-indole-7-acetic acid and the pharmaceutically acceptable salts thereof.

2,3-Dihydro-1-(3-hydroxy-4-methoxybenzoyl)-2-oxo-1H-indole-7-acetic acid and the pharmaceutically acceptable salts thereof.

2,3-Dihydro-2-oxo-1H-indole-7-acetic acid methyl ester.

2,3-Dihydro-2-oxo-1H-indole-7-acetic acid phenylmethyl ester.

2,3-Dihydro-2-oxo-1H-indole-7-propanoic acid methyl ester.

2,3-Dihydro-2-oxo-1H-indole-7-propanoic acid phenylmethyl ester.

1,2,3,4-Tetrahydro-2-oxo-8-quinolineactic acid ethyl ester.

1,2,3,4-Tetrahydro-2-oxo-8-quinolineactic acid phenylmethyl ester.

5 1,2,3,4-Tetrahydro-2-oxo-8-quinolinepropanoic acid ethyl ester.

1,2,3,4-Tetrahydro-2-oxo-8-quinolinepropanoic acid phenylmethyl ester.

10 1-(2-Chlorobenzoyl)-5-fluoro-2,3-dihydro-2-oxo-1H-indole-7-propanoic acid methyl ester.

1-(2-Fluorobenzoyl)-6-methoxy-1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic acid phenyl ester.

1-(2-Methoxybenzoyl)-1,2,3,4-tetrahydro-2-oxo-6-phenoxy-8-quinolinepropanoic acid and the pharmal5

15aceutically acceptable salts thereof.

1-(2-Methoxybenzoyl)-1,2,3,4-tetrahydro-2-oxo-6-phenoxy-8-quinolinepropanoic acid phenylmethyl ester.

2,3-Dihydro-2-oxo-1H-indole-7-acetamide.

20 2,3-Dihydro-2-oxo-N-4-pyridinyl-1H-indole-7-acetamide.

N-[2-[bis(1-methylethyl)amino]ethyl]-2,3-dihydro-2-oxo-1H-indole-7-acetamide.

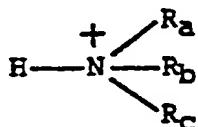
Also contemplated within the scope of the present invention are the compounds [(2,3-dihydro-2-oxo-1H-indole-7-yl)methyl]-propadioic acid and its dimethyl ester which are particularly useful as intermediates 25 in the preparation of compounds of formula I where x is zero and y is one.

The compounds of the present invention (structure 30 I where R₄ is hydroxyl) form salts with pharmaceutically acceptable metal or amine cations derived from organic and inorganic bases. The term "pharmaceutically acceptable metal cation" contemplates positively charged metal ions such as those derived 35 from sodium, potassium, calcium, magnesium, aluminum, iron, zinc, and the like.

The term "pharmaceutically acceptable amine cation" contemplates the positively charged ions derived from ammonia and organic nitrogenous bases strong enough to form such cations. Bases useful

5 for the formation of pharmaceutically acceptable non-toxic acid addition salts of compounds containing a carboxyl acid function form a class whose limits are readily understood by those skilled in the art.

Merely for illustration, this class of amines
10 can be said to comprise, in cationic form, those of
the formula:



15 wherein R_a , R_b , and R_c independently are hydrogen, alkyl of from one to six carbon atoms, cycloalkyl of from about three to six carbon atoms, aryl, aralkyl of from about seven to about ten carbon atoms, hydroxylalkyl of from two to four carbon atoms, or

20 monoarylhydroxylalkyl of from about eight to about fifteen carbon atoms. Further, when taken together with the nitrogen atom to which they are attached, any two of R_a , R_b , and R_c may form part of a five- or six-membered nitrogen-containing heterocyclic

25 aromatic or non-aromatic ring containing carbon or oxygen, said nitrogen-containing heterocyclic rings being unsubstituted, monosubstituted, or disubstituted with alkyl groups of from one to six carbon atoms.

30 Specific examples of organic amine cations contemplated as falling within the scope of the present invention include mono-, di-, and tri-methylammonium, mono-, di-, and triethylammonium,

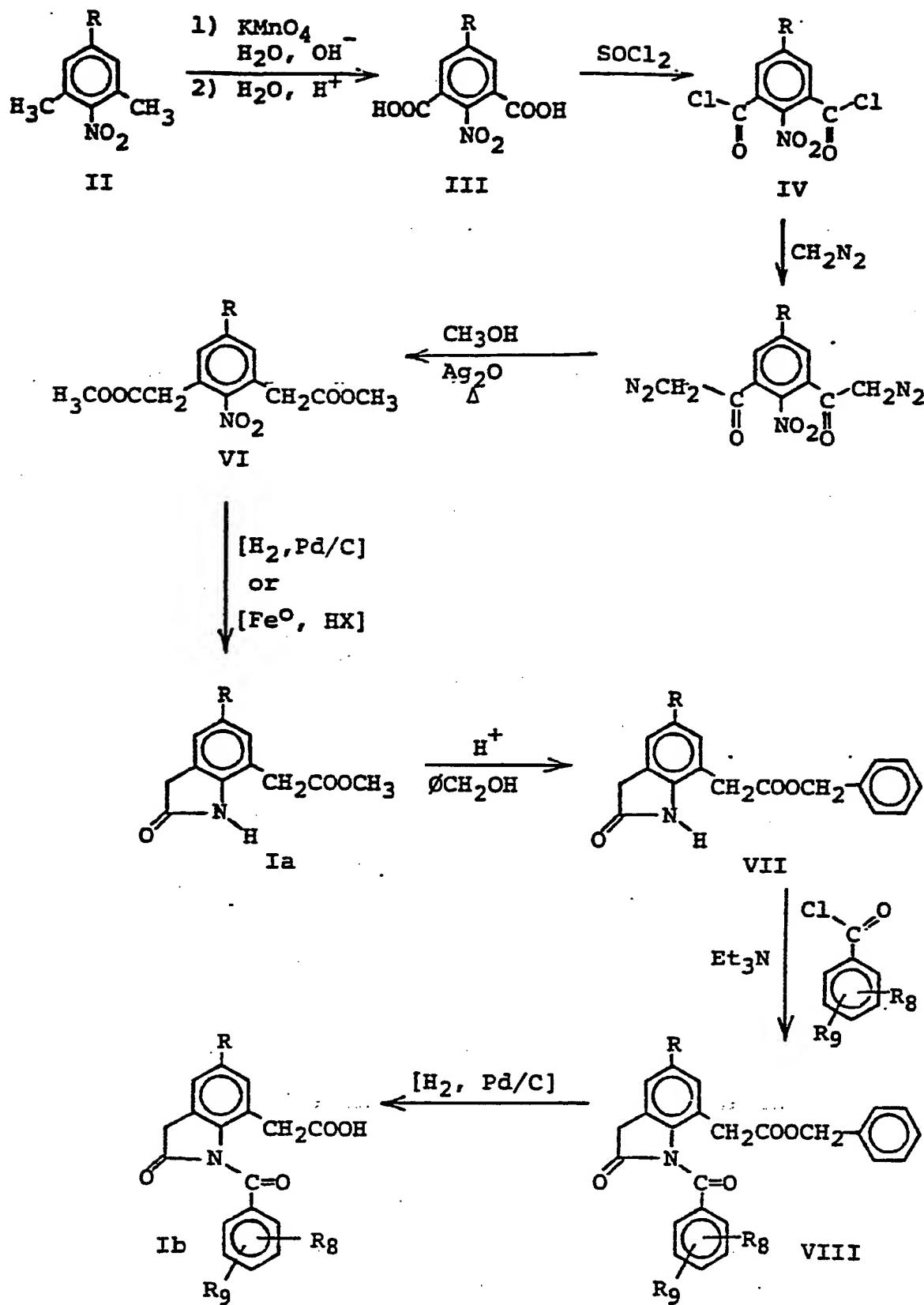
mono-, di-, and tripropylammonium (n-propyl and iso-propyl), ethyldimethylammonium, benzylammonium, dibenzylammonium, benzylidemethylammonium, cyclohexylammonium, piperidinium, morpholinium, pyrrolidinium, 5 4-ethylmorpholinium, 1-isopropylpyrrolidinium, 1,4-dimethylpiperazinium, 1-n-butylpiperidinium, 2-methylpiperidinium, 1-ethyl-2-methylpiperidinium, mono-, di-, and triethanolammonium, ethyldiethanolammonium, n-butylmonoethanolammonium, tris(hydroxymethyl)methyl-10 ammonium, phenylmonoethanolammonium, and the like.

The ammonium, amine, or metal salts are prepared by reaction of the appropriate acetic or propanoic acid compound of this invention with an equivalent amount of an organic amine base or an inorganic base 15 such as ammonium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, calcium carbonate, sodium bicarbonate, and the like in an appropriate solvent such as water or an aqueous alcohol, followed by removal of the solvent under 20 reduced pressure.

The free acid form of the compound may be regenerated from the salts, if desired, by contacting the salt with a dilute aqueous solution of an acid such as hydrochloric.

25 The compounds of formula I where both x and y are zero are prepared by the general method detailed in Reaction Scheme 1.

-10-
Reaction Scheme 1



Appropriately substituted 2,6-dimethyl-1-nitrobenzenes (II) are oxidized to the corresponding 2-nitro-1,3-benzenedicarboxylic acids (III) as described by E. Notting and C. Gachot, Chem. Ber., 39:73-75

5 (1906). The diacids (III) are converted to 2-nitrobenzenedicarbonyl chlorides (IV) by reaction with, for example, thionyl chloride in 1,1,2,2-tetrachloroethane.

The dicarbonyl chlorides (IV) are converted to 2-nitro-1,3-diazoacetylbenzenes (V) by reaction with,

10 for example, diazomethane in diethyl ether. The diazoacetylbenzene compounds (V) are converted to the corresponding dimethyl esters (VI) by the well-known Arndt-Eistert synthesis (see, for example W. E.

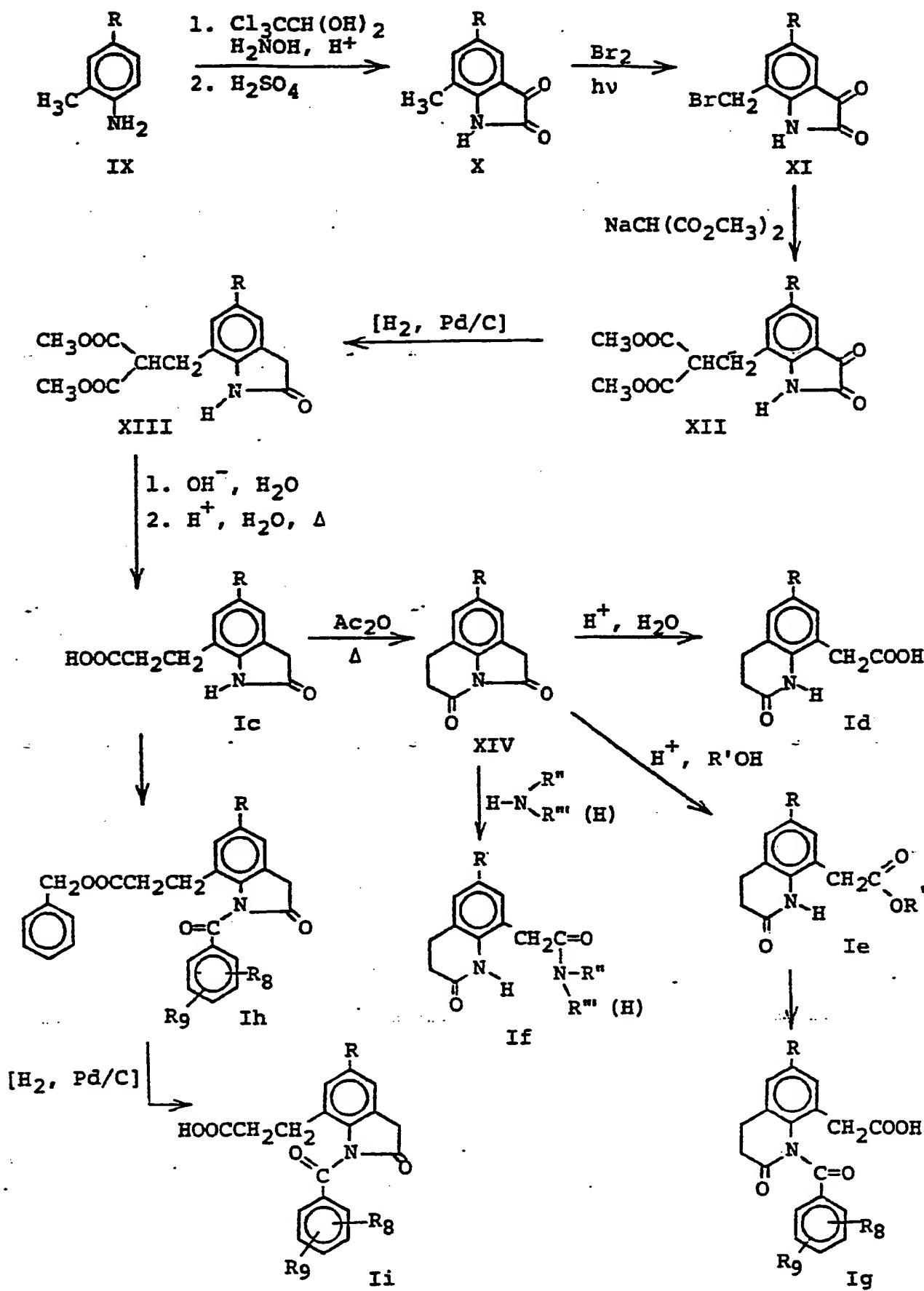
Bachmann and W. S. Struve, Organic Reactions, Volume

15 I, 38 (1942). Reduction of the diesters (VI) with, for example, hydrogen over palladium/carbon catalyst cyclizes the diesters to produce compounds Ia in accordance with formula I where both x and y are zero and R₄ is methoxy. These compounds can be converted,

20 if desired, to the free acids, to salts of the free acids, esters of other alcohols, or amides by conventional reactions well known to practitioners of the art.

The methyl esters, compounds Ia may be converted 25 to the free acids by hydrolysis, and thence further to their salts by conventional techniques or, alternatively, compounds Ia may be transformed into the phenylmethyl esters VII by transesterification. The phenylmethyl esters may be reacted with a substituted 30 or unsubstituted benzoyl chloride compound in, for example, toluene in the presence of a catalyst such as triethylamine, to produce the benzoylated derivatives compounds VIII. Hydrogenolysis of the compounds VIII yields the benzoylated free acid compounds Ib.

35 The compounds of formula I where x is zero and y is one, or vice versa, are prepared by the general methods detailed in Reaction Scheme 2.

-12-
Reaction Scheme 2

The known 4-substituted-2-methylanilines (IX) are converted to the corresponding 5-substituted-7-methyl-isatins (X) by the reaction described in A. Wahl et al., Ann. Chim., 5:323 (1926). The 5-chloro-7-methylisatin [H. Pajouhesh et al., J. Pharm. Sci., 72: 381-421 (1983)] and the 5-bromo-7-methylisatin [German Offenlegungsschrift DR 2,925,175] are known compounds.

The methyl group of the isatins (X) is subsequently photocatalytically halogenated by reaction 10 with, for example, bromine under ultraviolet light in an inert solvent such as dichloromethane containing a trace amount of water, to produce the 5-substituted-7-bromomethylisatins (XI):

Reaction of the 7-bromomethylisatins (XI) with 15 the sodio derivative of malonic acid dimethyl ester in, for example, tetrahydrofuran at 0°C produces the diesters (XII). Reduction of compounds XII with, for example, hydrogen over palladium/carbon catalyst yields compounds XIII. Saponification of the 20 diesters, XIII, in dilute aqueous base, followed by acidification and heating, results in decarboxylation to produce the monocarboxylic acid compounds Ic where x is zero, y is one, and R₄ is -OH.

The compounds Ic may be further converted, if 25 desired, to the tricyclic diones XIV by cyclization in acetic anhydride, and the resulting tricyclic dione compounds solvolyzed in dilute aqueous acid to yield the corresponding bicyclic lactam acids, Id, where x is one and y is zero, or solvolyzed in acidic 30 alcohol to produce the bicyclic lactam esters Ie. Similarly, compound XIV may be ring-opened by reaction with the desired alkylamine or dialkylamine to produce the bicyclic lactam amides If.

This reaction sequence is particularly useful 35 for the conversion of compounds in which the one of

the lactam rings in the tricyclic compound is a five-membered ring and the other is six-membered to compounds of formula I in which x is one and y is zero. Solvolysis in alcoholic solution, catalyzed 5 by a trace of acid, generally results in the formation of the product in which the smaller five-membered lactam ring is opened.

Compounds Ic or Id may be converted to their corresponding benzoylated or substituted-benzoylated 10 ester derivatives by first converting the compounds to their esters by conventional means, and subsequently reacting the esters with benzoyl chloride or an appropriately substituted benzoyl chloride in, for example, toluene in the presence of an acid acceptor 15 such as triethylamine.

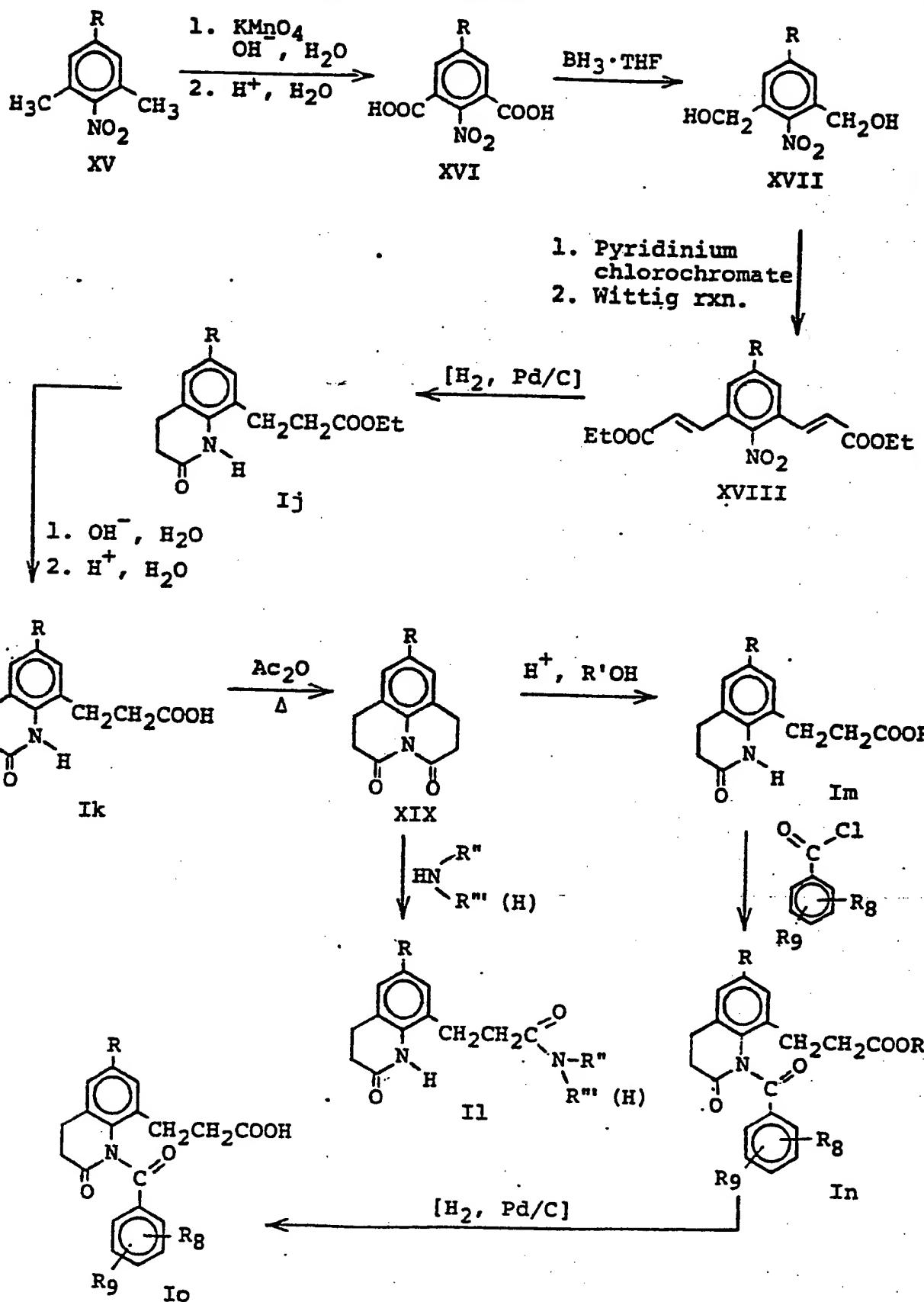
Compounds Ie, where R' is phenylmethyl may be similarly substituted with benzoyl or substituted-benzoyl and subsequently converted to the free acids Ig by conventional hydrogenolysis reaction.

20 In an analogous manner, the acid compound Ic can be converted to its phenylmethyl ester by conventional means and subsequently substituted with benzoyl or substituted-benzoyl. The benzoylated phenylmethyl ester Ih can be converted to the benzoylated free acid 25 II by hydrogenolysis.

The esters of free acid forms of the compounds are converted, if desired, to the corresponding salts, esters, or amides by conventional reactions known to those skilled in the art.

30 Compounds of formula I where both x and y are one are prepared by the general reaction sequence illustrated in Reaction Scheme 3.

Reaction Scheme 3



The 4-substituted-2,6-dimethylnitrobenzene compounds of formula XV, where R is hydrogen, fluorine, chlorine, or bromine, are oxidized, for example, by hot, aqueous, basic permanganate solution to the corresponding substituted isophthalic acid derivatives, XVI. These compounds are subsequently reduced, for example, by borane-tetrahydrofuran complex to the 4-substituted-2,6-bis(hydroxymethyl)-nitrobenzene compounds of formula XVII. The hydroxymethyl groups are oxidized to the corresponding aldehyde groups by a mild oxidizing reagent such as pyridinium chlorochromate, and the aldehydes are converted to the diesters, XVIII, by the well-known Wittig Reaction (c.f. U. Schollkopf, Angew. Chem., 71:260(1959)).

In the specific instance where R is fluorine, the dialcohol compounds of formula XVII, or the diesters of formula XVIII may be conveniently converted to compounds where R is alkoxy of from one to six carbon atoms, phenoxy, phenylmethoxy, or dialkylamino of from one to six carbon atoms by reaction with the appropriate alcohol or dialkylamine in dimethylformamide in the presence of potassium carbonate.

Catalytic reduction of the resulting compounds by hydrogen reduces both the nitro group and the carbon-carbon unsaturation and cyclizes one lactam ring to produce compounds of formula Ij where x and y are both one, and R₄ is ethoxy. Saponification of the esters, Ij, in dilute base followed by acidification produces the acids, Ik, which may be used as such or converted, if desired, to pharmaceutically acceptable salts, esters, or amides by conventional techniques well known to practitioners of the art.

The acids, Ik, may be converted directly to the esters, Im, by conventional means, or cyclized to the tricyclic dione compounds XIX in acetic anhydride. In a preferred method of making the esters, Im, the

resulting tricyclic dione compounds may be solvolyzed in the appropriate alcohols. Alternatively, compound XIX may be ring-opened by reaction with the appropriate alkylamine or dialkylamine to produce the 5 bicyclic lactam amides II.

The esters, I_m, may be converted to their benzoylated derivatives, I_n, in a manner similar to that previously described. The benzoylated phenyl-methyl esters may be converted to the benzoylated 10 free acids, I_o, by conventional hydrogenolysis.

The acids, I_o, may be converted to desired salts, esters, or amides by conventional reactions well known to practitioners of organic chemical art.

Also in accordance with the present invention, 15 pharmaceutical compositions may be produced by formulating compounds having structural formula I above in unit dosage form with a pharmaceutically acceptable carrier. Some examples of unit dosage forms are tablets, capsules, lozenges, and pills; as well as 20 powders and aqueous and nonaqueous solutions and suspensions packaged in containers containing either one, or some larger number of dosage units and capable of being subdivided into individual doses by such means as measurement into a teaspoon or other standard 25 container.

Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are sugars such as lactose and sucrose; starches such as corn starch and potato starch; cellulose derivatives such 30 as sodium carboxymethylcellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; 35 propylene glycol; glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; as well as other

compatible substances normally employed in pharmaceutical formulations.

The pharmaceutical compositions of this invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These latter materials, if present, are generally used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents, including other cognition activating agents such as 10 3-phenoxyypyridine, and N-[N'N'-diisopropylaminoethyl] pyrrolidine-2-oxo-1-acetamide.

The percentage of active ingredient in the foregoing compositions can be varied within wide limits, but for practical purposes, the active ingredient is 15 preferably present in a concentration of a least 10% in a solid composition, and at least 2% in a primarily liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present. The pharmaceutical 20 compositions of this invention contain from 0.1 to 250.0 mg, preferably from 1 to 75 mg of the active ingredient per dosage unit so that the entire amount to be administered during a day can be made from a reasonable number of dose units.

25 The compounds of the present invention may exist as solids in anhydrous form as well as forms which are solvated with water, alcohols, and other pharmaceutically acceptable solvents. These solid forms may be incorporated into formulations intended for 30 parenteral administration. Such formulations may be either in solution form or in powdered form intended for combination with an isotonic solution containing other ingredients such as preservatives, etc.

The solid forms of the compounds of this invention may also be incorporated into suppository for-

mulations intended for rectal administration or into syrup formulations intended for oral administration.

The mammalian dose range for a 70 kg subject is from 1 to 1500 mg of compound per day, preferably

5 between about 25 mg to 750 mg per day, optionally administered in portions.

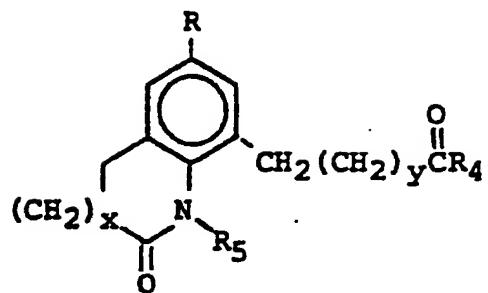
The compounds of the present invention are useful for treating senility or for reversing amnesia.

The effectiveness of these compounds was evaluated by 10 a test designed to show the ability of a given substance to reverse amnesia induced by electro-convulsive shock. The test is more fully described in United States Patent 4,154,347, issued March 20, 1979, and incorporated herein by reference. The 15 only differences between the tests conducted in the present case and that described in the referenced patent were that in the present case, the test compounds were administered orally and the duration of the electrical shock used to induce amnesia in the 20 test animals was 1.0 second.

The data from tests conducted employing compounds of the present invention appear in the Table I. The following criteria were used in interpreting the data:

40% or more amnesia reversal in the test animals = 25 active, A; 25% to 39% amnesia reversal = borderline activity, C; 0% to 24% reversal of amnesia = inactive, N.

TABLE I



Percent Amnesia Reversal of Orally Administered
Test Compounds (In Mice)

Compound	x	y	R	R ₄	R ₅	Dose (mg/kg of Body Weight)		
						100	10	1
A	0	0	H	OH	H	54(A)	58(A)	60(A)
B	0	0	H	OCH ₃	H	92(A)	33(C)	42(A)
C	1	1	H	OC ₂ H ₅	H	13(N)	0(N)	25(C)

The following representative examples are provided to enable one skilled in the art to practice the present invention. These examples are merely illustrative of the preparation of compounds in accordance with the present invention and are not to be read as limiting the scope of the invention as defined by the appended claims.

EXAMPLE 1

Preparation of 2-nitro-1,3-benzenediacetic acid
dimethyl ester

2,6-dimethyl-1-nitrobenzene is oxidized to 2-nitro-1,3-benzenediacrylic acid as described by E. Notting and C. Gachot; Chem. Ber., 39, 73-75 (1906) to yield 2-nitro-1,3-benzenediacrylic acid. A suspension of 2-nitro-1,3-benzenediacrylic acid (25 g, 0.118 mole) in 1,1,2,2-tetrachloroethane (100 ml) is treated with thionyl chloride (30 ml) and the mixture refluxed seven hours. The mixture is concentrated at reduced pressure and after recrystallization from n-heptane yields pure 2-nitro-1,3-benzenediacarbonyl chloride, mp 129-131.5°C. A solution of diazomethane (4.2 g, 0.1 mole) in diethyl ether (500 ml) is cooled to 0°C and 2-nitro-1,3-benzenediacarbonyl chloride (2.93 g, 0.0118 mole) is added in portions. The mixture is stirred 17 hours and concentrated at reduced pressure to yield 2-nitro-1,3-diazoacetylbenzene as a tan solid. The 2-nitro-1,3-diazoacetylbenzene is dissolved in methanol (250 ml) and the solution is added to freshly prepared silver oxide (synthesized by the reaction of 5 ml of a 10% silver nitrate solution with sodium hydroxide). The mixture is stirred at 0°C for one hour and at 55-60°C for two hours. The solution is filtered and concentrated to yield crude 2-nitro-1,3-benzenediacetic acid dimethyl ester. Recrystallization from n-heptane yields pure 2-nitro-1,3-benzenediacetic acid dimethyl ester, mp 144-145°C.

Preparation of 2,3-dihydro-2-oxo-1H-indole-7-acetic acid methyl ester.

A solution of 2-nitro-1,3-benzenediacetic acid dimethyl ester (5.98 g, 0.022 mole) in tetrahydrofuran and methanol (2:1, 100 ml) is treated with hydrogen gas in the presence of 20% Pd/C for 18 hours. The mixture is filtered and concentrated at reduced pressure to yield 2,3-dihydro-2-oxo-1H-indole-7-acetic acid methyl ester. Final purification is accomplished using flash chromatography on silica (elution with 1:19 methanol:dichloromethane) and results in pure 2,3-dihydro-2-oxo-1H-indole-7-acetic acid methyl ester, mp 156-157°C.

EXAMPLE 2

15 Preparation of 2,3-dihydro-2-oxo-1H-indole-7-acetic acid.

A solution of 2,3-dihydro-2-oxo-1H-indole-7-acetic acid methyl ester (2.05 g, 0.01 mole) in methanol (50 ml) is treated with 1 N sodium hydroxide (10 ml, 0.01 mole) and the mixture is heated at 60°C for one hour. The reaction is concentrated at reduced pressure to yield the sodium salt of 2,3-dihydro-2-oxo-1H-indole-7-acetic acid. The sodium salt is dissolved in 2:1 water:methanol and the solution is passed over a Dowex 50X-8 ion exchange resin. The eluate is concentrated at reduced pressure to yield pure 2,3-dihydro-2-oxo-1H-indole-7-acetic acid, mp 234-236°C.

Preparation of 7-methylisatin

In a 5 l flask is placed chloral hydrate (90 g, 0.54 mole) and water (1200 ml). To this solution is 5 added sodium sulfate decahydrate (1300 g, 10.9 mole) followed by a solution of o-methylaniline (54 g, 0.5 mole) in water (300 ml) containing concentrated hydrochloric acid (43 ml, 0.5 mole). Then a solution of hydroxylamine hydrochloride (110 g, 1.58 mole) in 10 water (50 ml) is added. The reaction mixture is heated to reflux over a 90 minute period and refluxed 15 minutes. The reaction is cooled in ice and the resulting crystalline ortho-isonitrosoacetotoluidide is isolated by filtration and air dried. The ortho- 20 isonitrosoacetotoluidide is dissolved in portions in concentrated sulfuric acid (325 ml) that is preheated to 50°C with vigorous stirring. The reaction temperature is maintained under 75°C. When the addition is complete, the mixture is heated at 80°C for 30 25 minutes, cooled, and poured unto ice (3 kg). The 7-methylisatin is isolated by filtration. The 7-methylisatin is purified by dissolution in dilute sodium hydroxide. The basic solution is treated with 4 N hydrochloric acid until a slight amount of 30 precipitation is evident. The mixture is filtered and the filtrate is acidified. The pure 7-methylisatin is recovered by filtration and dried in vacuo at 80°C and 0.1 mm pressure, mp 270-273°C (A. Wahl, et al., Ann. Chim. 5 323 (1926); reported mp 267°C.

30 Preparation of 7-bromomethylisatin

The 7-methylisatin (16.1 g, 0.1 mole) is suspended in dichloroethane (2000 ml) and the suspension is heated and irradiated with a high intensity light source to the reflux point. Bromine (24.3 g, 0.15 35 mole) is added dropwise over a one hour period.

The solution is filtered hot and concentrated at reduced pressure to yield the product as an orange solid after washing with anhydrous diethyl ether.

5 The product is purified using flash chromatography on silica (elution with 24:1 dichloromethane:diethyl ether) to afford after drying (at 60°C at 0.1 mm); 7-bromomethylisatin, mp 199-200°C dec.

Preparation of 2,3-dihydro-2,3-dioxo-1H-indole-7-

10 propandioic acid dimethyl ester

A solution of dimethylmalonate (15.7 ml, 0.138 mole) in tetrahydrofuran is cooled to 0°C and sodium hydride (50% in mineral oil) (6.5 g, 0.138 mole) is added portionwise over 15 minutes.

15 The reaction is stirred at 0°C for 30 minutes and a suspension of 7-bromomethylisatin (15.0 g, 0.0625 mole) in tetrahydrofuran (50 ml) is added in one portion. The resulting deep purple solution is stirred at room temperature for 30 minutes. 1.2 N 20 hydrochloric acid is added until the mixture turns clear yellow and the solution is concentrated at reduced pressure to 20% of the original volume. The solution is extracted with dichloromethane (2 x 300 ml). The combined extracts are dried 25 (MgSO₄), filtered, and concentrated to yield a yellow solid. This is purified by flash chromatography on silica (elution with 9:1 dichloromethane:diethyl ether) to afford after concentration pure 2,3-dihydro-2,3-dioxo-1H-indole-7-propandioic acid 30 dimethyl ester, mp 137-140°C.

EXAMPLE 4

Preparation of 2,3-dihydro-2-oxo-1H-indole-7-propandioic acid dimethyl ester

A solution of 2,3-dihydro-2,3-dioxo-1H-indole-7-propandioic acid dimethyl ester (1.4 g, 0.0048 mole) is dissolved in acetic acid (100 ml) and in the presence of 20% Pd/C is treated with hydrogen gas at 50 psi. The solution is filtered and concentrated to yield 2,3-dihydro-2-oxo-1H-indole-7-propandioic acid dimethyl ester. This is purified by flash chromatography on silica (elution with 7:3 hexane: ethyl acetate) to give after concentration pure 2,3-dihydro-2-oxo-1H-indole-7-propandioic acid dimethyl ester, mp 161-161.5°C.

15

EXAMPLE 5

Preparation of 2,3-dihydro-2-oxo-1H-indole-7-propanoic acid

A solution of 2,3-dihydro-2-oxo-1H-indole-7-propandioic acid dimethyl ester (4.6 g, 0.0166 moles) is dissolved in methanol (50 ml) and 1 N sodium hydroxide (33.2 ml, 0.0332 mole) is added. The mixture is stirred at 50°C for 90 minutes then concentrated at reduced pressure. The residue is dissolved in water (75 ml) and methanol (50 ml). The solution is made acidic with excess Dowex 50X-8 acidic ion exchange resin and heated with stirring at 70°C for 24 hours. The solution is cooled, filtered, and concentrated to dryness to yield 2,3-dihydro-2-oxo-1H-indole-7-propanoic acid. The 2,3-dihydro-2-oxo-1H-indole-7-propanoic acid is purified by flash chromatography on silica (elution with 9:1 dichloromethane:methanol) NMR spectra: (¹H-CDCl₃) δ 7.30-7.10 (m, 3H), δ 6.50-6.25 (b, 1H) δ 3.80-3.70 (m, 2H), δ 3.70 (s, 2H), δ 3.28-3.22 (m, 2H).

Preparation of 2-nitro-1,3-benzenedimethanol

A solution of 2-nitro-1,3-benzeneddicarboxylic acid (12.7 g, 0.06 mole) in tetrahydrofuran (60 ml) 5 is cooled to 0°C and 1 N borane:tetrahydrofuran (300 ml, 0.3 mole) is added dropwise over one hour. The mixture is allowed to warm slowly to 25°C and is stirred for 36 hours. Methanol (50 ml) is added slowly, the mixture is filtered and evaporated. The 10 residue is dissolved in ethyl acetate (100 ml) and washed with water (25 ml), dried ($MgSO_4$), filtered, and evaporated to yield a yellow solid. This is further purified by flash chromatography over silica (elution with 1:1 hexane:ethyl acetate) to afford 15 after concentration pure 2-nitro-1,3-benzenedi-methanol, mp 100-101°C.

Preparation of 2-nitro-1,3-benzenediacrylic acid diethyl ester

A solution of 2-nitro-1,3-benzenedimethanol 20 (5.0 g, 0.027 mole) in dichloromethane (90 ml) is mixed with anhydrous sodium acetate (10 g). The mixture is cooled to 0°C and pyridinium chlorochromate (4.0 eq, 21.4 g, 0.1 mole) is added portionwise over 10 minutes. The reaction is allowed to warm to room 25 temperature over six hours. The mixture is poured into diethyl ether (1 l) and filtered through Florosil. The colorless solution is concentrated at reduced pressure and azeotroped with heptane to remove pyridine. The resulting oil is reasonably pure 30 2-nitro-1,3-benzenedialdehyde and is used as is.

The 2-nitro-1,3-benzenedialdehyde (3.4 g, 0.019 mole) is dissolved in toluene (60 ml) and carbethoxymethylene triphenylphosphorane (19.2 g, 0.06 mole) is added. The mixture is heated at 60°C 35 for eight hours, cooled, and concentrated at reduced

pressure. Diethyl ether (100 ml) is added and the mixture is filtered. The filtrate is concentrated and purified by flash chromatography over silica (elution with 4:1 hexane:ethyl acetate) to afford, 5 after concentration, pure 2-nitro-1,3-benzenediacrylic acid diethyl ester, mp 114-115°C.

Preparation of 1,2,3,4-Tetrahydro-2-oxo-8-quinoline-propanoic acid ethyl ester

A solution of 2-nitro-1,3-benzenediacrylic acid 10 diethyl ester (3.5 g, 0.011 mole) in absolute ethanol (100 ml) is treated with hydrogen at 1 atmosphere pressure for 12 hours in the presence of 20% Pd/C. The mixture is filtered and concentrated at reduced pressure to yield 1,2,3,4-tetrahydro-2-oxo-8- 15 quinolinepropanoic acid ethyl ester, mp 102-103°C.

EXAMPLE 7

Preparation of 1,2,3,4-tetrahydro-2-oxo-8-quinoline-propanoic acid

A solution of 1,2,3,4-tetrahydro-2-oxo-8- 20 quinolinepropanoic acid ethyl ester (2.5 g, 0.01 mole) in methanol (50 ml) is treated with 0.5 N sodium hydroxide solution (19.5 ml, 0.00975 mole) and the mixture is heated at 50°C for two hours. The mixture is concentrated at reduced pressure to yield the 25 sodium salt of 1,2,3,4-tetrahydro-2-oxo-8- quinolinepropanoic acid as a solid. The sodium salt of 1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic acid is dissolved in 2:1 water: methanol (5 ml) and the solution is passed over a Dowex 50X-8 ion exchange 30 column and the solution is concentrated at reduced pressure to yield 1,2,3,4-tetrahydro-2-oxo-8- quinolinepropanoic acid, mp 164-165°C.

Preparation of 5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinoline-2,4(1H)-dione

A solution of 2,3-dihydro-2-oxo-1H-indole-7-
5 propanoic acid (2.0 g, 0.0098 mole) in acetic
anhydride (8 ml) is heated to 90°C with stirring for
one hour. Excess acetic anhydride is removed at
reduced pressure. The red crystalline material is
purified by flash chromatography over silica (elution
10 with 23:2 dichloromethane:diethyl ether). Final
purification by fractional sublimation yields 5,6-
dihydro-4H-pyrrolo[3,2,1-ij]quinoline-2,4(1H)-dione,
mp 194-197°C.

Preparation of 1,2,3,4-tetrahydro-2-oxo-8-quinoline-acetic acid ethyl ester

A solution of 5,6-dihydro-4H-pyrrolo [3,2,1-ij]-
quinoline-2,4(1H)-dione (1.87 g, 0.01 mole) in ethanol
(10 ml) is treated with a drop of concentrated
hydrochloric acid. The mixture is refluxed 24 hours
20 (or until the dione starting material can no longer be
detected by thin layer chromatography). The solution
is cooled and concentrated at reduced pressure. The
product is purified by flash chromatography to yield
1,2,3,4-tetrahydro-2-oxo-8-quinoline acetic acid ethyl
25 ester.

EXAMPLE 9

Preparation of 1,2,3,4-tetrahydro-2-oxo-8-quinoline-acetic acid

A solution of 5,6-dihydro-4H-pyrrolo[3,2,1-ij]-
30 quinoline-2,4(1H)-dione (1.87 g, 0.01 mole) in water
(10 ml) is treated with a drop of concentrated
hydrochloric acid. The mixture is refluxed 24 hours

(or until the starting dione can no longer be detected by thin layer chromatography). The solution is cooled, and concentrated at reduced pressure. The product is purified by flash chromatography to yield

5 1,2,3,4-tetrahydro-2-oxo-8-quinoline acetic acid.

EXAMPLE 10

Preparation of 1,2,6,7-tetrahydro-3H,5H-benzo[ij]-quinolizine-3,5-dione

1,2,3,4-Tetrahydro-2-oxo-8-quinolinepropanoic acid (2.1 g, 0.0096 mole) is dissolved in acetic anhydride (10 ml) and the solution is heated to 100°C for one hour. Excess acetic anhydride is removed at reduced pressure and the residual anhydride is removed by addition of toluene and repeated concentration.

15 The solid is recrystallized from ethyl acetate to yield pure 1,2,6,7-tetrahydro-3H,5H-benzo[ij]-quinolizine-3,5-dione, mp 136-140°C.

Preparation of 1,2,3,4-tetrahydro-2-oxo-8-quinoline-propanoic acid phenylmethyl ester

20 A solution of 1,2,6,7-tetrahydro-3H,5H-benzo[ij]-quinolizine-3,5-dione (20.1 g, 0.1 mole) in phenylmethanol (200 ml) is treated with a drop of concentrated hydrochloric acid. The mixture is refluxed 24 hours (or until the starting dione can no longer be detected by thin layer chromatography). The solution is cooled and concentrated at reduced pressure. The product is purified by flash chromatography to yield 1,2,3,4-tetrahydro-2-oxo-8-quinoline propanoic acid phenylmethyl ester.

Preparation of 1-(4-methoxybenzoyl)-1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic acid phenylmethyl ester

5 A solution of 1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic phenylmethyl ester (30.4 g, 0.1 mole) in toluene is treated with 4-methoxybenzoyl-chloride (17.1 g, 0.1 mole). The solution is stirred and heated to 70°C and a solution of triethylamine

10 10.1 g, 0.1 mole) in toluene (100 ml) is added drop-wise. Heating and stirring is continued for 18 hours. The warm mixture is filtered through filter aid and concentrated at reduced pressure. Purification by flash chromatography on silica (elution with methanol:

15 dichloromethane, 1:19) yields 1-(4-methoxybenzoyl)-1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic and phenylmethyl ester.

EXAMPLE 12

Preparation of 1-(4-methoxybenzoyl)-1,2,3,4-tetra-

20 hydro-2-oxo-8-quinolinepropanoic acid

A solution of 1-(4-methoxybenzoyl)-1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic acid phenylmethyl ester (10 g, 0.023 mole) is dissolved in tetrahydroferan (250 ml) and 1 g of 20% Pd/C is added. The mixture is shaken under an atmosphere of H₂ gas until H₂ absorption is complete. The mixture is filtered and concentrated at reduced pressure to yield after trituration with anhydrous diethylether and drying, 1-(4-methoxybenzoyl)-1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic acid.

EXAMPLE 13

Preparation of 2,3-dihydro-2-oxo-1H-indole-7-acetic acid phenylmethyl ester

A solution of 20.5 g of 2,3-dihydro-2-oxo-1H-indole-7-acetic acid (0.1 mole) and 4.0 g (0.1 mole) of sodium hydroxide in 200 ml of water is vigorously stirred together with a solution of 20.5 g (0.12 mole) of benzyl bromide and 3.4 g (0.1 mole) of tetrabutylammonium bromide in 300 ml of toluene.

10 The mixture is heated with stirring at 85°C for three hours. After cooling, the toluene layer is separated and the aqueous layer is extracted twice with dichloromethane (300 ml portions). The combined extracts are dried over anhydrous magnesium sulfate, 15 filtered and concentrated at reduced pressure. Final purification of the product is accomplished using flash chromatography on silica gel (elution with 1:19 methanol:dichloromethane) to yield 2,3-dihydro-2-oxo-1H-indole-acetic acid phenylmethyl ester.

20

EXAMPLE 14

Preparation of 2,3-dihydro-1-(4-methoxybenzoyl)-2-oxo-1H-indole-7-acetic acid phenylmethyl ester

A solution of 28.1 g (0.1 mole) 2,3-dihydro-2-oxo-1H-indole-7-acetic acid phenylmethyl ester in 25 400 ml of toluene is treated with 17.1 g (0.1 mole) of 4-methoxybenzoyl chloride. The mixture is heated at 70°C with stirring and a solution of 10.2 g (0.1 mole) of triethylamine in 100 ml of toluene is added dropwise.

30 The mixture is stirred with heating for an additional 16 hours, filtered while warm through filter aid to remove triethylammonium hydrochloride, and concentrated at reduced pressure.

Chromatography over silica gel (elution with 1:19 methanol:dichloromethane) yields, after concentration, 2,3-dihydro-1-(4-methoxybenzoyl)-2-oxo-1H-indole-7-acetic acid phenylmethyl ester.

5

EXAMPLE 15

Preparation of 2,3-dihydro-1-(4-methoxybenzoyl)-2-oxo-1H-indole-7-acetic acid

A solution of 29.5 g (0.1 mole) 2,3-dihydro-1-(4-methoxybenzoyl)-2-oxo-1H-indole-7-acetic acid

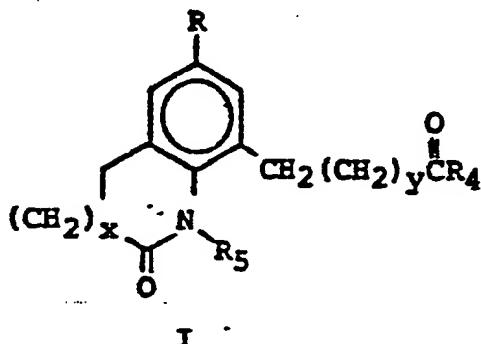
10 phenylmethyl ester in tetrahydrofuran is reduced with hydrogen over 2 g of 20% Pd/C catalyst. After the theoretically calculated amount of hydrogen has been consumed, the solution is filtered through filter aid. The filtrate is concentrated at reduced

15 pressure and the oily residue is triturated with anhydrous diethyl ether to yield 2,3-dihydro-1-(4-methoxybenzoyl)-2-oxo-1H-indole-7-acetic acid.

CLAIMS (for BE,CH,DE,FR,GB,IT,LI,LU,NL,SE):

1. A compound having the following general formula I

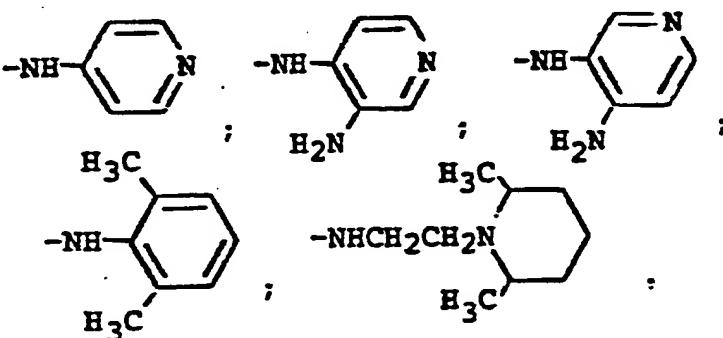
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15 wherein x and y are, independently, zero or one;
 wherein R is a hydrogen atom; a halogen atom; a hydroxyl radical; -OR₁ where R₁ is an alkyl radical of from one to six carbon atoms, a phenyl radical or a phenylmethyl radical; or
 20 -NR₂R₃ where R₂ and R₃ are, independently, an alkyl radical of from one to six carbon atoms;
 wherein R₄ is a hydroxy radical or the pharmaceutically acceptable metal, ammonium or amine acid addition salt thereof; -OR₁, where
 25 R₁ is as defined above;

30

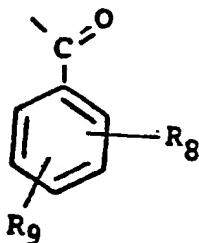


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-NHCH₂CH₂N[CH(CH₃)₂]₂; or -NR₆R₇ where R₆ and R₇ are, independently, a hydrogen atom or an alkyl radical of from one to six carbon atoms; and

wherein R_5 is a hydrogen atom;

5



10

where R_8 and R_9 are, independently, a hydrogen atom, a halogen atom, a hydroxyl radical, $-OR_1$ where R_1 is as defined above, $NR_{10}R_{11}$ where R_{10} and R_{11} are, independently, a hydrogen atom or 15 an alkyl radical of from one to six carbon atoms, or R_8 and R_9 , when taken together and attached to adjacent carbon atoms, are $-OCH_2O-$.

2. A compound according to Claim 1, wherein x and y are both zero.

3. A compound according to Claim 1, wherein x and y are both one.

4. A compound according to Claim 1, wherein x is zero and y is one.

5. A compound according to Claim 1, wherein 25 x is one and y is zero.

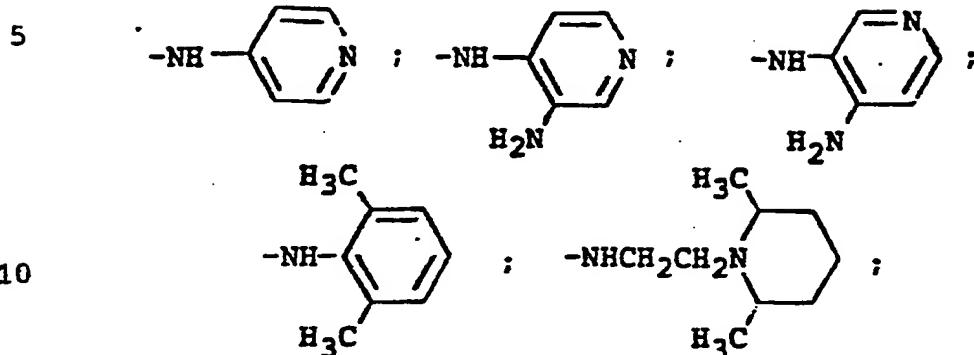
6. A compound according to any preceding claim, wherein R is a hydrogen atom; a fluorine atom; a chlorine atom; a hydroxy radical; $-OR_1$ where R_1 is an alkyl radical of from one to six 30 carbon atoms, a phenyl radical, or a phenylmethyl radical; or $-NR_2R_3$ where R_2 and R_3 are, independently, an alkyl radical of from one to six carbon atoms.

7. A compound according to any preceding claim, wherein R_4 is a hydroxy radical or a 35 pharmaceutically acceptable salt thereof.

8. A compound according to any one of Claims 1 to 6, wherein R_4 is $-OR_1$ where R_1 is

as defined in Claim 1.

9. A compound according to any one of Claims 1 to 6, wherein R_4 is



15 $-\text{NHCH}_2\text{CH}_2\text{N}[\text{CH}(\text{CH}_3)_2]_2$; or $-\text{NR}_6\text{R}_7$ where R_6 and R_7 are, independently, a hydrogen atom or an alkyl radical of from one to six carbon atoms.

10. A compound according to Claim 1, having the name:

20 2,3-dihydro-2-oxo-1H-indole-7-acetic acid;

2,3-dihydro-1-(3-methoxybenzoyl)-2-oxo-1H-indole-7-acetic acid;

2,3-dihydro-1-(4-methoxybenzoyl)-2-oxo-1H-indole-7-acetic acid;

25 2,3-dihydro-1-(4-methoxybenzoyl)-2-oxo-1H-indole-7-propanoic acid;

1-[4-(dimethylamino)benzoyl]-1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic acid;

1-[4-methoxy-3-(phenylmethoxy)benzoyl]-

30 1,2,3,4-tetrahydro 2-oxo-8-quinolinepropanoic acid;

1-(1,3-benzodioxol-5-ylcarbonyl)-1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic acid;

2,3-dihydro-1-(4-hydroxy-3-methylbenzoyl)-

35 2-oxo-1H-indole-7-acetic acid;

2,3-dihydro-2-oxo-1H-indole-7-propanoic acid;

1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic acid;
1-(4-methoxybenzoyl)-1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic acid;
5 1-benzoyl-2-3-dihydro-2-oxo-1H-indole-7-acetic acid;
2,3-dihydro-1-(3-hydroxy-4-methoxybenzoyl)-2-oxo-1H-indole-7-acetic acid;
10 2,3-dihydro-2-oxo-1H-indole-7-acetic acid methyl ester;
2,3-dihydro-2-oxo-1H-indole-7-acetic acid phenylmethyl ester;
2,3-dihydro-2-oxo-1H-indole-7-propanoic acid methyl ester;
15 2,3-dihydro-2-oxo-1H-indole-7-propanoic acid phenylmethyl ester;
1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic acid ethyl ester;
20 1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic acid phenylmethyl ester;
1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic acid ethyl ester;
25 1-(2-chlorobenzoyl)-5-fluoro-2,3-dihydro-2-oxo-1H-indole-7-propanoic acid methyl ester;
1-(2-fluorobenzoyl)-6-methoxy-1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic acid phenyl ester;
30 1-(2-methoxybenzoyl)-1,2,3,4-tetrahydro-2-oxo-6-phenoxy-8-quinolinepropanoic acid;
1-(2-methoxybenzoyl)-1,2,3,4-tetrahydro-2-oxo-6-phenoxy-8-quinolinepropanoic acid phenyl ester;
35 2,3-dihydro-2-oxo-1H-indole-7-acetamide;

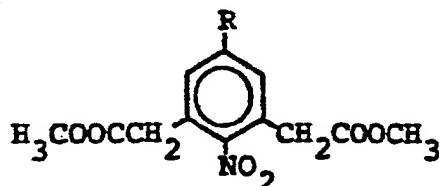
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2,3-dihydro-2-oxo-N-4-pyridinyl-1H-indole-7-acetamide;
N-[2-[bis(1-methylethyl)amino]ethyl]-2,3-dihydro-2-oxo-1H-indole-7-acetamide.

5 11. A compound useful as an intermediate for the preparation of compounds in accordance with claim 1, wherein x is zero and y is one, said compound having the name: [(2,3-dihydro-2-oxo-1H-indole-7-yl)methyl]propadioic acid dimethyl ester.

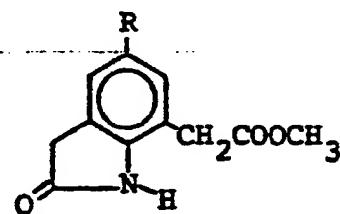
10 12. A method of preparing a compound of structure I, according to claim 1, wherein both x and y are zero, said method comprising the steps of
a) reducing a compound having the formula

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wherein R is as defined in Claim 1,
to form a bicyclic lactam ester of the formula

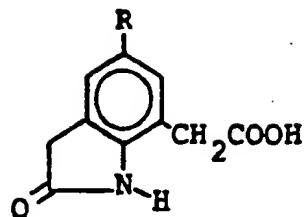
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b) subsequently converting, if desired, said bicyclic lactam ester to a bicyclic lactam acid of the formula

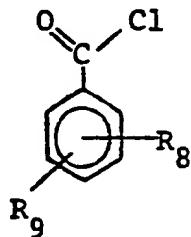
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15 by hydrolysis and subsequent acidification and forming the pharmaceutically acceptable salts thereof by conventional means; or

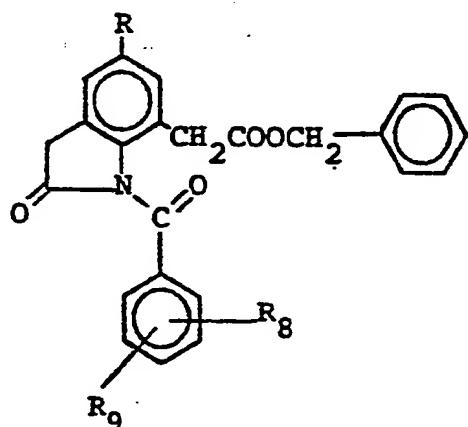
c) alternatively, converting, if desired, said bicyclic lactam ester product of step a) to the phenylmethyl ester by conventional means;

20 d) subsequently reacting, if desired, the bicyclic lactam phenylmethyl ester of step c) with a compound of the formula



25

wherein R₈ and R₉ are independently hydrogen, halogen, hydroxy; -OR₁ where R₁ is alkyl of from one to six carbon atoms, phenylmethyl; -NR₁₀R₁₁ where R₁₀ and R₁₁ are independently hydrogen or alkyl of from one to six carbon atoms; or when taken together and attached to adjacent carbon atoms, R₈ and R₉ are -OCH₂O-; to form a compound having the formula



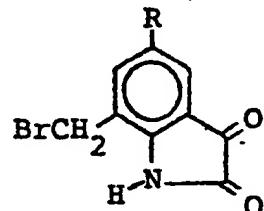
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- e) converting the product of step d), if desired, to the free acid by hydrogenolysis; and
- f) converting the free acid product of step e), if desired, to its salts, esters, or amides by conventional means.

13. A method of preparing a compound of structure I according to claim 1, wherein x is zero and y is one, said method comprising the steps of

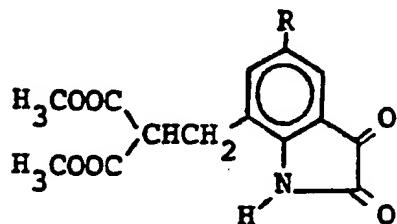
- a) converting a 5-substituted-7-bromomethyl-isatin compound of the formula

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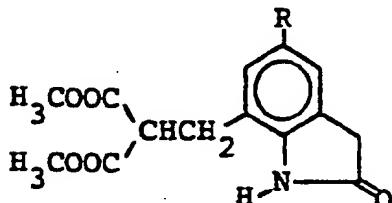
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wherein R is as previously defined in claim 1, with the sodio derivative of dimethylmalonate to form a malonate derivative of the formula



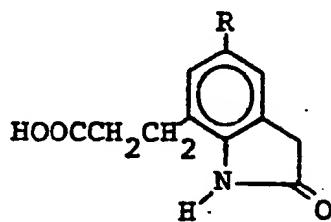
b) reducing said malonate derivative of step a) with hydrogen over a catalyst to produce a bicyclic lactam diester of the formula

15



c) subsequently saponifying, acidifying and heating to decarboxylate the product of step b to form a bicyclic lactam acid of the formula

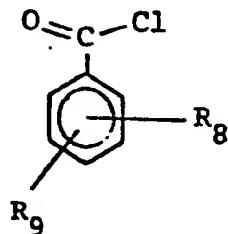
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d) subsequently converting, if desired, said bicyclic lactam acid compound to the phenylmethyl ester by conventional means;

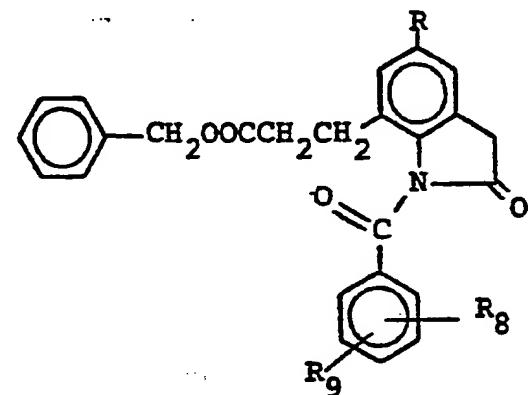
e) subsequently reacting, if desired, the phenylmethyl ester product of step d) with a compound of the formula



30

wherein R₈ and R₉ are independently hydrogen; halogen; hydroxyl; -OR₁ where R₁ is alkyl of from one to six carbon atoms, phenyl, or benzyl; -NR₁₀R₁₁ where R₁₀ and R₁₁ are independently hydrogen, alkyl of from one to six carbon atoms; or when taken together, and attached to adjacent carbon atoms, R₈ and R₉ are -OCH₂O-; to form a benzoylated compound of the formula;

35



40

f) converting the product of step e), if desired, to the free acid

45

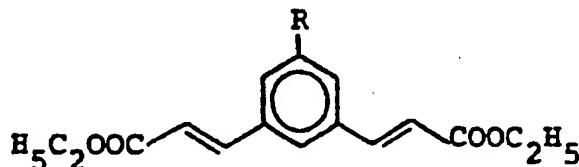
by hydrogenolysis; and

g) converting the free acid product of step f), if desired, to its salts, esters, or amides by conventional means.

14. A method of preparing a compound of structure I according to claim 1, wherein both x and y are one, said method comprising the steps of

- reducing a compound having the structure

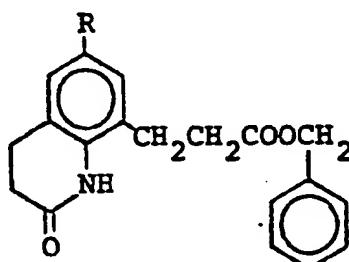
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wherein R is as defined in Claim 1;
to form a bicyclic lactam ester having the
formula

10

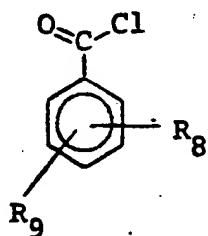
- subsequently converting, if desired, said
bicyclic lactam ester product of step a)
to the phenylmethyl ester



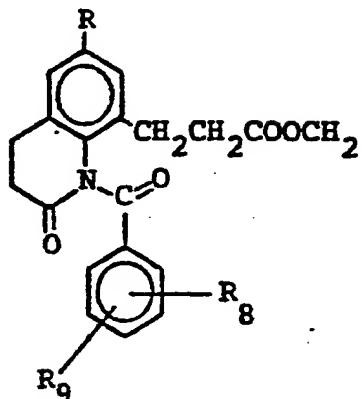
15

by conventional means;

- subsequently reacting, if desired, the phenylmethyl ester product of step b) with a
compound having the formula



to form a compound having the formula



20 wherein R_8 and R_9 are as defined in Claim 1;

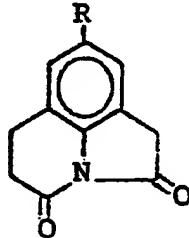
 d) converting the phenylmethyl ester product
 of step c) to the free acid by hydro-
 genolysis; and

 e) further converting said free acid, if
 desired, to its salts, esters, or amides
 by conventional means.

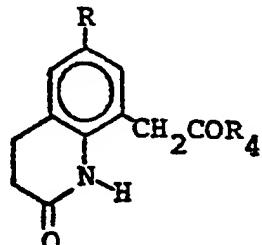
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15. A method of preparing a compound of structure I
according to claim 1, wherein x is one and y is
zero, said method comprising the steps of

a) solvolyzing a compound having the structure

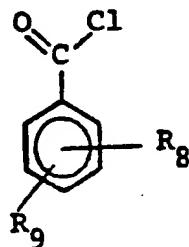


wherein R is as defined in Claim 1;
by reaction with water, an alcohol in the
presence of a catalytic amount of acid
or amine to produce a bicyclic lactam
compound of the formula

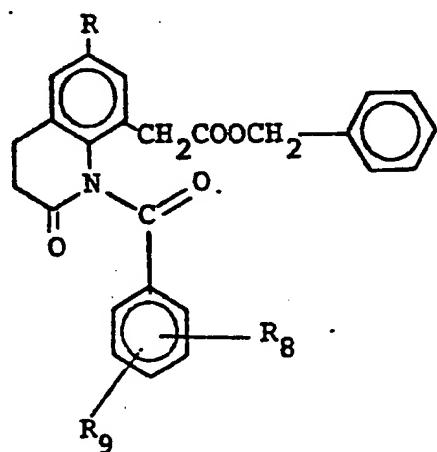


wherein R_4 is as previously defined in
claim 1;

15 b) subsequently reacting, if desired, the
product of step a) wherein R_4 is phenyl-
methoxy, with a compound of the formula

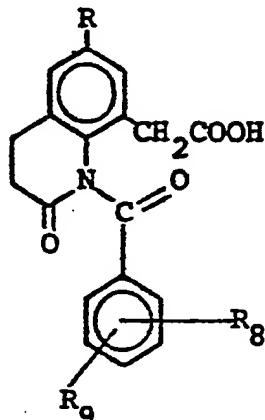


20 wherein R_8 and R_9 are independently
hydrogen; halogen; hydroxyl; $-OR_1$ where
 R_1 is alkyl of from one to six carbon
atoms, phenyl, or benzyl; $-NR_{10}R_{11}$
where R_{10} and R_{11} are independently
hydrogen, alkyl of from one to six carbon
atoms; or when taken together, and
25 attached to adjacent carbon atoms, R_8 and
 R_9 are $-OCH_2O-$; to form a compound of
the formula



c) converting the phenylmethyl ester product of step b) or step a) to the free acid

30



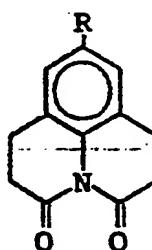
by hydrogenolysis;

d) further converting said free acid, if desired, to its salts, esters, or amides by conventional means.

16. A method of preparing a compound of structure I according to claim 1, wherein both x and y are one, said method comprising the steps of

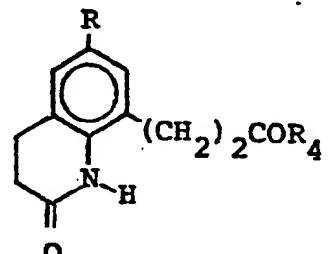
a) solvolyzing a compound having the structure

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wherein R is as defined in Claim 1 by reaction with water, an alcohol in the presence of a catalytic amount of acid, or an amine to produce a bicyclic lactam compound of the formula

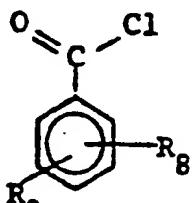
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wherein R4 is as defined above;

b) subsequently reacting, if desired, the product of step a) wherein R₄ is phenylmethoxy, with a compound of the formula

15

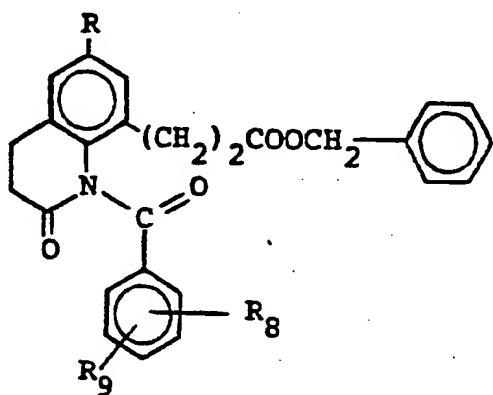


wherein R₈ and R₉ are independently hydrogen; halogen; hydroxyl; -OR₁ where R₁ is alkyl of from one to six carbon atoms, phenyl, or phenylmethyl; -NR₁₀R₁₁

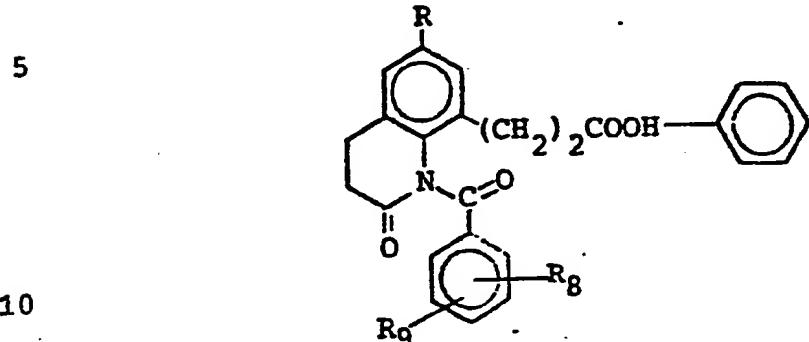
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where R₁₀ and R₁₁ are independently hydrogen, alkyl of from one to six carbon atoms; or when taken together, and attached to adjacent carbon atoms, R₈ and R₉ are -OCH₂O-; to form a compound of the formula

25



c) converting the phenylmethyl ester product of step b) or step a) to the free acid



15 by hydrogenolysis; and

d) further converting said free acid, if desired, to its salts, esters, or amides by conventional means.

17. A pharmaceutical composition useful
20 for treating senility or for reversing the effects of amnesia in a mammal comprising an effective amount of a compound as claimed in any preceding claim in combination with a pharmaceutically acceptable carrier or diluent.

25

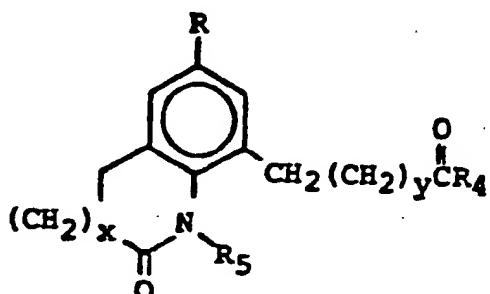
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CLAIMS (for AT):

1. A process for producing a compound having the following general formula I

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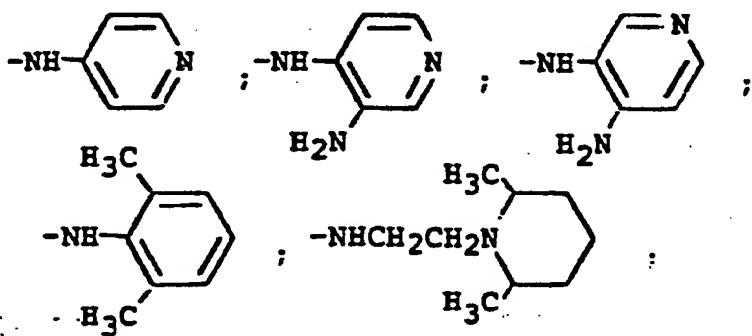


10

I

wherein x and y are, independently, zero or one;
15 wherein R is a hydrogen atom; a halogen atom; a hydroxyl radical; -OR₁ where R₁ is an alkyl radical of from one to six carbon atoms, a phenyl radical or a phenylmethyl radical; or -NR₂R₃ where R₂ and R₃ are, independently, an alkyl radical of from one to six carbon atoms;
20 wherein R₄ is a hydroxy radical or the pharmaceutically acceptable metal, ammonium or amine acid addition salt thereof; -OR₁, where R₁ is as defined above;

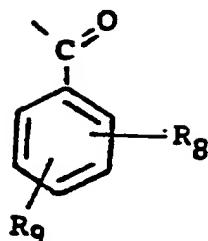
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35 -NHCH₂CH₂N[CH(CH₃)₂]₂; or -NR₆R₇ where R₆ and R₇ are, independently, a hydrogen atom or an alkyl radical of from one to six carbon atoms; and wherein R₅ is a hydrogen atom;

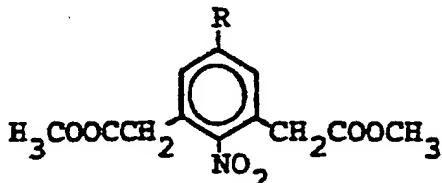
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10 where R₈ and R₉ are, independently, a hydrogen atom, a halogen atom, a hydroxyl radical, -OR₁ where R₁ is as defined above, NR₁₀R₁₁ where R₁₀ and R₁₁ are, independently, a hydrogen atom or an alkyl radical of from one to six carbon atoms
15 or R₈ and R₉, when taken together and attached to adjacent carbon atoms, are -OCH₂O;
which process comprises, when both x and y are zero, the steps of
a) reducing a compound having the formula

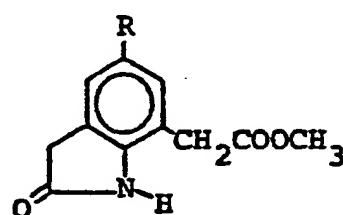
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wherein R is as defined above
to form a bicyclic lactam ester of the
formula

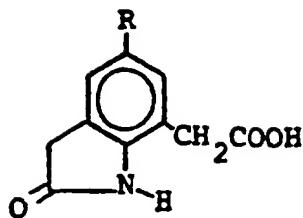
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b) subsequently converting, if desired, said bicyclic lactam ester to a bicyclic lactam acid of the formula

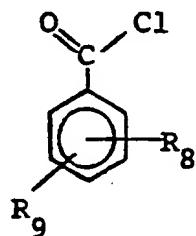
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by hydrolysis and subsequent acidification
and forming the pharmaceutically acceptable
salts thereof by conventional means; or

10 c) alternatively, converting, if desired, said
bicyclic lactam ester product of step a) to
the phenylmethyl ester by conventional means;
d) subsequently reacting, if desired, the
bicyclic lactam phenylmethyl ester of step c)
15 with a compound of the formula

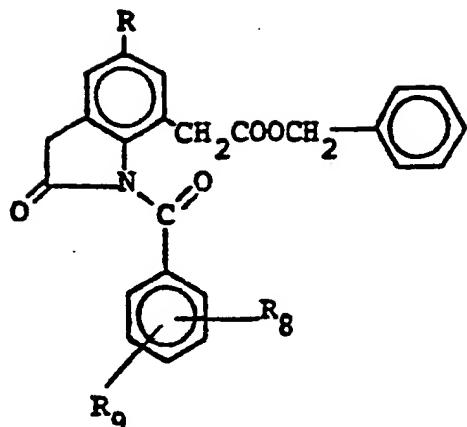
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wherein R8 and R9 are independently hydrogen
halogen, hydroxy; -OR1 where R1 is alkyl of
from one to six carbon atoms, phenylmethyl;
-NR10R11 where R10 and R11 are
independently hydrogen or alkyl of from one
to six carbon atoms; or when taken together
and attached to adjacent carbon atoms, R8
30 and R9 are -OCH2O-; to form a compound
having the formula

35

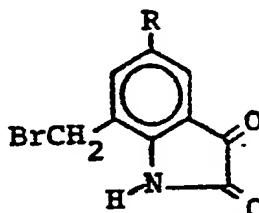


e) converting the product of step d), if desired, to the free acid by hydrogenolysis; and
f) converting the free acid product of step e), if desired, to its salts, esters, or amides by conventional means;

15 or which process comprises, when x is zero and y is one, the steps of

a) converting a 5-substituted-7-bromomethyl-isatin compound of the formula

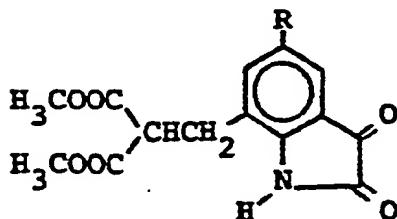
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wherein R is as previously defined, with the sodio derivative of dimethylmalonate to form a malonate derivative of the formula

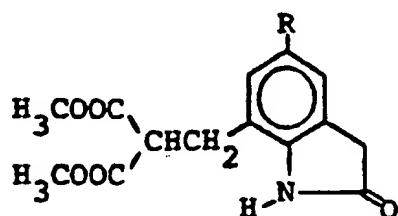
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b) reducing said malonate derivative of step a) with hydrogen over a catalyst to produce a bicyclic lactam diester of the formula

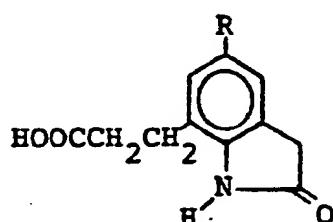
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c) subsequently saponifying, acidifying and heating to decarboxylate the product of step b to form a bicyclic lactam acid of the formula

15

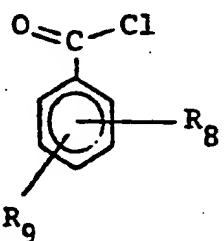


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d) subsequently converting, if desired, said bicyclic lactam acid compound to the phenyl-methyl ester by conventional means:

e) subsequently reacting, if desired, the phenylmethyl ester product of step d) with a compound of the formula

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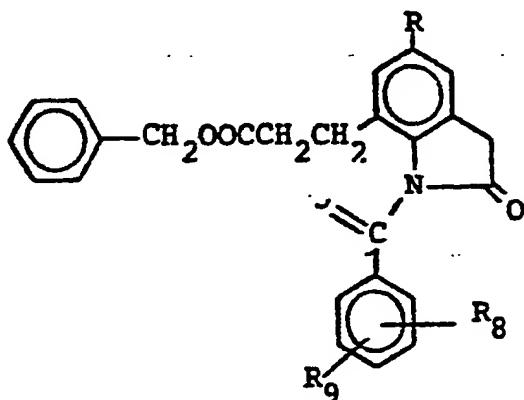
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wherein R₈ and R₉ are independently hydrogen; halogen; hydroxyl; -OR₁ where R₁ is alkyl of from one to six carbon atoms, phenyl, or benzyl; -NR₁₀R₁₁ where R₁₀ and R₁₁ are independently hydrogen, alkyl of from one to six carbon atoms, phenyl, or benzyl; and R₁₂ is alkyl of from one to six carbon atoms, phenyl, or benzyl.

atoms; or when taken together, and attached to adjacent carbon atoms, R₈ and R₉ are -OCH₂O-; to form a benzoylated compound of the formula;

5

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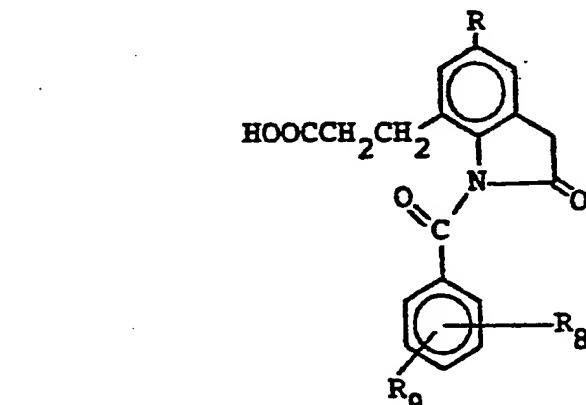
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f) converting the product of step e), if desired, to the free acid

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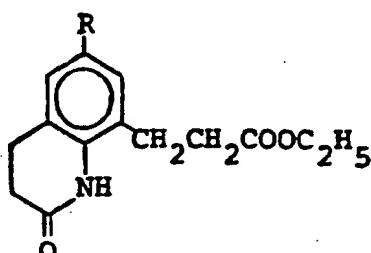
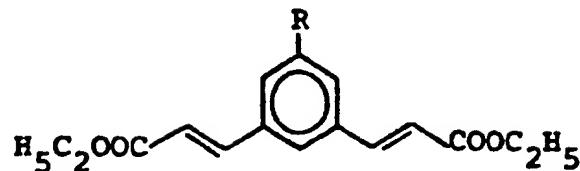


by hydrogenolysis; and

g) converting the free acid product of step f), if desired, to its salts, esters, or amides by conventional means;

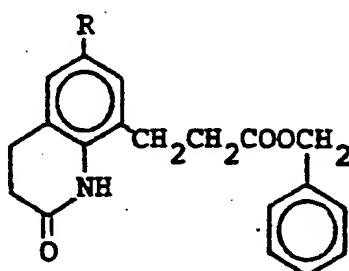
or which process comprises, when both x and y are one, the steps of

a) reducing a compound having the structure



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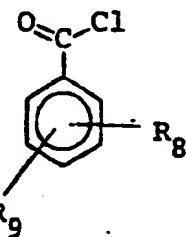
b) subsequently converting, if desired, said
bicyclic lactam ester product of step a)
to the phenylmethyl ester



by conventional means;

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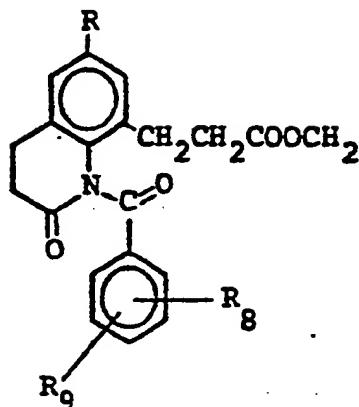
c) subsequently reacting, if desired, the phenyl-
methyl ester product of step b) with a
compound having the formula



wherein R8 and R9 are as defined above

to form a compound having the formula

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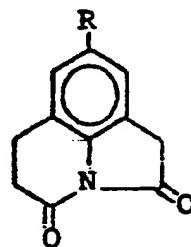
d) converting the phenylmethyl ester product of step c) to the free acid by hydro-

15 genolysis; and

e) further converting said free acid, if desired, to its salts, esters, or amides by conventional means;

or which process comprises, when x is one
20 and y is zero, the steps of
a) solvolyzing a compound having the structure

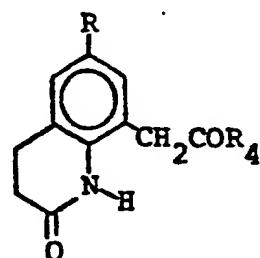
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wherein R is as defined above
by reaction with water, an alcohol in the
presence of a catalytic amount of acid
or amine to produce a bicyclic lactam
compound of the formula

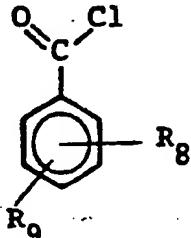
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wherein R_4 is as previously defined;

5 b) subsequently reacting, if desired, the product of step a) wherein R_4 is phenyl-methoxy, with a compound of the formula

10



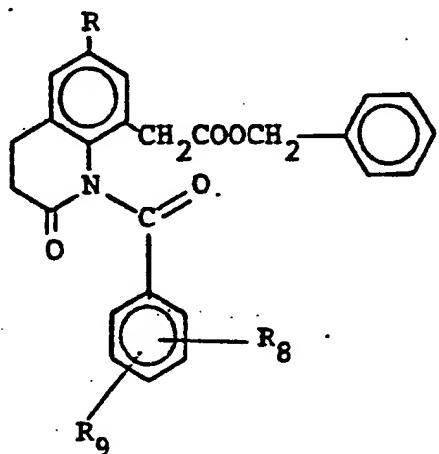
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wherein R_8 and R_9 are independently hydrogen; halogen; hydroxyl; $-OR_1$ where R_1 is alkyl of from one to six carbon atoms, phenyl, or benzyl; $-NR_{10}R_{11}$ where R_{10} and R_{11} are independently hydrogen, alkyl of from one to six carbon atoms; or when taken together, and attached to adjacent carbon atoms, R_8 and R_9 are $-OCH_2O-$; to form a compound of the formula

25

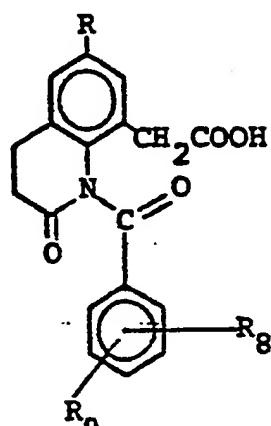
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c) converting the phenylmethyl ester product of step b) or step a) to the free acid

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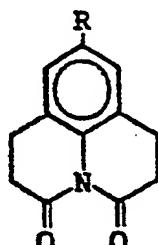
by hydrogenolysis;

15 d) further converting said free acid, if desired, to its salts, esters, or amides by conventional means;

or which process comprises, when both x and y are one, the steps of

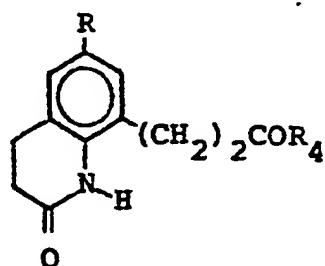
20 a) solvolyzing a compound having the structure

25



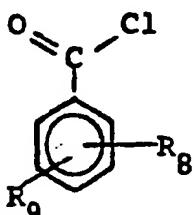
wherein R is as defined above
by reaction with water, an alcohol in the presence of a catalytic amount of acid, or an
30 amine to produce a bicyclic lactam compound of the formula

35



b) subsequently reacting, if desired, the product of step a) wherein R₄ is phenylmethoxy, with a compound of the formula

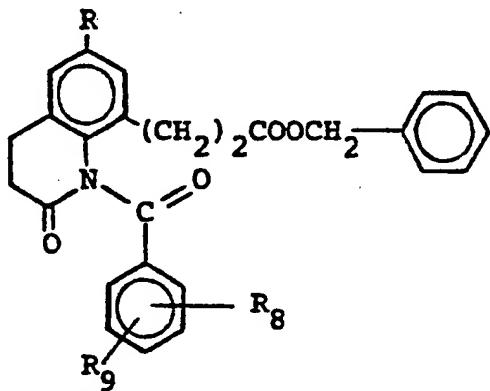
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wherein R₈ and R₉ are independently hydrogen; halogen; hydroxyl; -OR₁ where R₁ is alkyl of from one to six carbon atoms, phenyl, or phenylmethyl; -NR₁₀R₁₁ where R₁₀ and R₁₁ are independently hydrogen, alkyl of from one to six carbon atoms; or when taken together, and attached to adjacent carbon atoms, R₈ and R₉ are -OCH₂O-; to form a compound of the formula

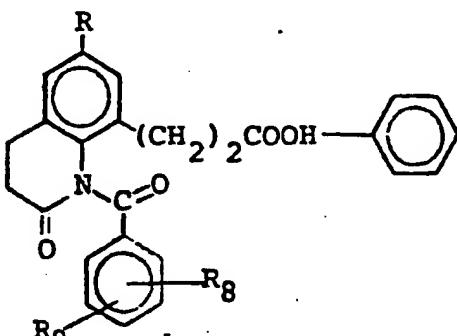
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c) converting the phenylmethyl ester product of step b) or step a) to the free acid

30



35

by hydrogenolysis; and

d) further converting said free acid, if desired, to its salts, esters, or amides by conventional means.

2. A process according to Claim 1, wherein 5 x and y are both zero.

3. A process according to Claim 1, wherein x and y are both one.

4. A process according to Claim 1, wherein x is zero and y is one.

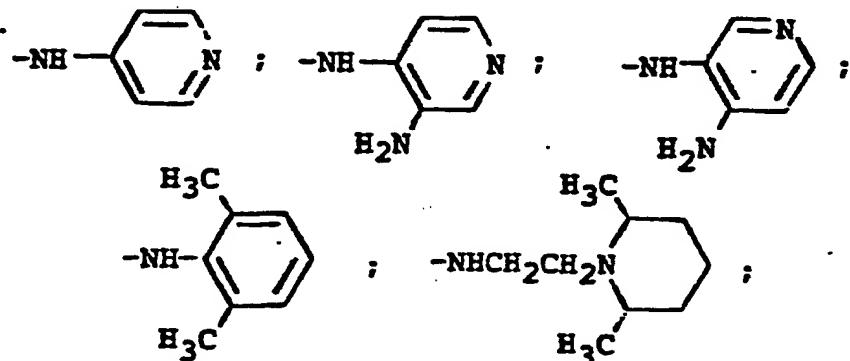
10 5. A process according to Claim 1, wherein x is one and y is zero.

6. A process according to any preceding claim, wherein R is a hydrogen atom; a fluorine atom; a chlorine atom; a hydroxy radical; -OR₁ 15 where R₁ is an alkyl radical of from one to six carbon atoms, a phenyl radical, or a phenylmethyl radical; or -NR₂R₃ where R₂ and R₃ are, independently, an alkyl radical of from one to six carbon atoms.

7. A process according to any preceding 20 claim, wherein R₄ is a hydroxy radical or a pharmaceutically acceptable salt thereof.

8. A process according to any one of Claims 1 to 6, wherein R₄ is -OR₁ where R₁ is as defined in Claim 1.

9. A process according to any one of 25 Claim 1 to 6, wherein R₄ is



30

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$-\text{NHCH}_2\text{CH}_2\text{N}[\text{CH}(\text{CH}_3)_2]_2$; or $-\text{NR}_6\text{R}_7$ where R_6 and R_7 are, independently, a hydrogen atom or an alkyl radical of from one to six carbon atoms.

10. A process according to Claim 1, for
5 producing a compound having the name:
2,3-dihydro-2-oxo-1H-indole-7-acetic acid;
2,3-dihydro-1-(3-methoxybenzoyl)-2-oxo-1H-
indole-7-acetic acid;
2,3-dihydro-1-(4-methoxybenzoyl)-2-oxo-1H-
10 indole-7-acetic acid;
2,3-dihydro-1-(4-methoxybenzoyl)-2-oxo-1H-
indole-7-propanoic acid;
1-[4-(dimethylamino)benzoyl]-1,2,3,4-
tetrahydro-2-oxo-8-quinolineacetic acid;
15 1-[4-methoxy-3-(phenylmethoxy)benzoyl]-
1,2,3,4-tetrahydro 2-oxo-8-quinolinepropanoic
acid;
1-(1,3-benzodioxol-5-ylcarbonyl)-1,2,3,4-
tetrahydro-2-oxo-8-quinolinepropanoic acid;
20 2,3-dihydro-1-(4-hydroxy-3-methylbenzoyl)-
2-oxo-1H-indole-7-acetic acid;
2,3-dihydro-2-oxo-1H-indole-7-propanoic acid;
1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic
acid;
25 1-(4-methoxybenzoyl)-1,2,3,4-tetrahydro-2-
oxo-8-quinolineacetic acid;
1-benzoyl-2-3-dihydro-2-oxo-1H-indole-
7-acetic acid;
30 2,3-dihydro-1-(3-hydroxy-4-methoxybenzoyl)-
2-oxo-1H-indole-7-acetic acid;
2,3-dihydro-2-oxo-1H-indole-7-acetic acid
methyl ester;
2,3-dihydro-2-oxo-1H-indole-7-acetic acid
35 phenylmethyl ester;
2,3-dihydro-2-oxo-1H-indole-7-propanoic acid
methyl ester;

2,3-dihydro-2-oxo-1H-indole-7-propanoic acid

phenylmethyl ester;

1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic

acid ethyl ester;

5 1,2,3,4-tetrahydro-2-oxo-8-quinolineacetic

acid phenylmethyl;

1,2,3,4-tetrahydro-2-oxo-8-quinolinepro-

panoic acid ethyl ester;

1,2,3,4-tetrahydro-2-oxo-8-quinolinepro-

10 panoic acid phenylmethyl ester;

1-(2-chlorobenzoyl)-5-fluoro-2,3-dihydro-2-

oxo-1H-indole-7-propanoic acid methyl ester;

1-(2-fluorobenzoyl)-6-methoxy-1,2,3,4-

tetrahydro-2-oxo-8-quinolineacetic acid phenyl

15 ester;

1-(2-methoxybenzoyl)-1,2,3,4-tetrahydro-2-

oxo-6-phenoxy-8-quinolinepropanoic acid;

1-(2-methoxybenzoyl)-1,2,3,4-tetrahydro-2-

oxo-6-phenoxy-8-quinolinepropanoic acid phenyl-

20 methyl ester;

2,3-dihydro-2-oxo-1H-indole-7-acetamide;

2,3-dihydro-2-oxo-N-4-pyridinyl-1H-indole-7-

acetamide;

N-[2-[bis(1-methylethyl)amino]ethyl]-2,3-

25 dihydro-2-oxo-1H-indole-7-acetamide.

11. A process for producing a compound,

useful as an intermediate in the process of Claim

1 where x is zero and y is one, the compound

having the name: [(2,3-dihydro-2-oxo-1H-indole-

7-yl)methyl]propandoic acid dimethyl ester;

which process preferably comprises reducing a compound

having the name [(2,3-dihydro-2,3-dioxo-1H-indole-7-

yl)methyl]-propandoic acid dimethyl ester.

12. A process for preparing a pharmaceutical

35 composition useful for treating senility or for

reversing the effects of amnesia in a mammal,

which process comprises combining a compound

-63-

produced by a process as claimed in any preceding
claim together with a pharmaceutically acceptable
carrier or diluent.

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